American Journal of Hematology 60:80–85 (1999)

LETTERS AND CORRESPONDENCE

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Platelet Cold Agglutinins and Cardiac Surgery Hypothermia

To the Editor: Ethylenediaminetetraacetic acid (EDTA)-independent pseudothrombocytopenia caused by platelet clumping is a relatively rare phenomenon that occurs in vitro in samples anticoagulated either with EDTA or sodium citrate [1]. Platelet clumping is caused by the presence of naturally occurring immunoglobulin (Ig)M antiplatelet autoantibodies (IgG are instead prevalent in patients with EDTA-dependent pseudothrombocytopenia), and occurs only in the presence of a calcium-chelating anticoagulant, and temperatures less than 37°C; by acting in concert, these two conditions modify the platelet membrane thus exposing cryptoantigens, and making them accessible to the antibody bond [2]. A slight fall in temperature can be crucial, because the phenomenon is observable in the laboratory even at room temperatures of 30–33°C. For this reason, it was recently questioned what would happen to an affected individual when subjected to hypothermia [3]. We report the first case of platelet cold agglutinins in a patient who successfully underwent cardiac surgery hypothermia.

A 60-year-old man with a ten-year history of hypertensive cardiopathy, was admitted to the coronary intensive care unit with unstable angina due to severe stenosis of the left anterior descending artery, and scheduled for multiple bypass surgery. Hematological examinations of EDTA-anticoagulated blood performed with an automated cell counter revealed a typical picture of pseudothrombocytopenia, with a platelet count of 17×10^9/L. Microscopic examination of the smear showed the presence of numerous platelet clumps that were also observed in subsequent samples of either EDTA or citrate-anticoagulated blood. When blood was instead collected by means of the Unopette Reagent System (Beckton-Dickinson, Rutherford, NJ) that utilizes ammonium oxalate as the anticoagulant-lysis solution, and platelets were counted at the light microscope, platelet clumping was no longer observed, and the platelet count was 386×10^9/L. An antiplatelet antibody assay gave a very strong positive reaction for IgM antibodies.

The patient underwent subsequent cardiac surgery in hypothermia at 30°C; three arterial-saphenous vein by-pass grafts to the internal mammary artery, right coronary artery, and the marginal branch of the two autologous vein grafts were inserted. The intervention went well, and no problems related to in vivo platelet clumping occurred.

To our knowledge, this is the first report of a patient with pseudothrombocytopenia due to platelet cold agglutinins who underwent hypothermia. The absence of complications confirms that platelet clumping caused by cold agglutinins, even in the presence of a fall in temperature, occurs only in the presence of structural alterations in the platelet membrane caused by calcium-chelating substances (EDTA or citrate), and therefore only in vitro. Moreover, in these cases, the definitive way to obtain a correct platelet count is to read samples anticoagulated with ammonium oxalate in a Burker chamber.

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The $--^{\mathrm{THAI}}$ and $--^{\mathrm{FIL}}$ Determinants of α Thalassemia in Taiwan

To the Editor. Alpha thalassemia is common throughout all tropical and subtropical regions of the world and most frequently results from the deletion of one ($-\alpha$) or both ($--$) *cis*-linked α genes on chromosome 16. Infants who inherit no α genes (genotype $--/--$) from their parents (genotype $--/\alpha\alpha$) have the hemoglobin (Hb) Bart's hydrops fetalis syndrome. Such infants die as a result of severe anemia late in gestation or at birth and the condition is associated with a high maternal morbidity. These problems can be avoided by judicious genetic counseling and prenatal diagnosis based on the previous characterization of the underlying molecular defects [1].

The Hb Bart's hydrops fetalis syndrome occurs most commonly in Southeast Asia where the predominant severe determinant of α thalassemia is the $--^{\mathrm{SEA}}$ defect. Two less common determinants are the $--^{\mathrm{FIL}}$ and $--^{\mathrm{THAI}}$ mutations both of which remove the embryonic ζ-globin gene as well as the α genes [2]. Homozygotes for these defects ($--^{\mathrm{FIL}}/--^{\mathrm{FIL}}$ and $--^{\mathrm{THAI}}/--^{\mathrm{THAI}}$) almost certainly die very early in gestation because they cannot produce any embryonic Hb. However, compound heterozygotes (e.g., $--^{\mathrm{FIL}}/--^{\mathrm{SEA}}$) have the classic form of Hb Bart's hydrops fetalis

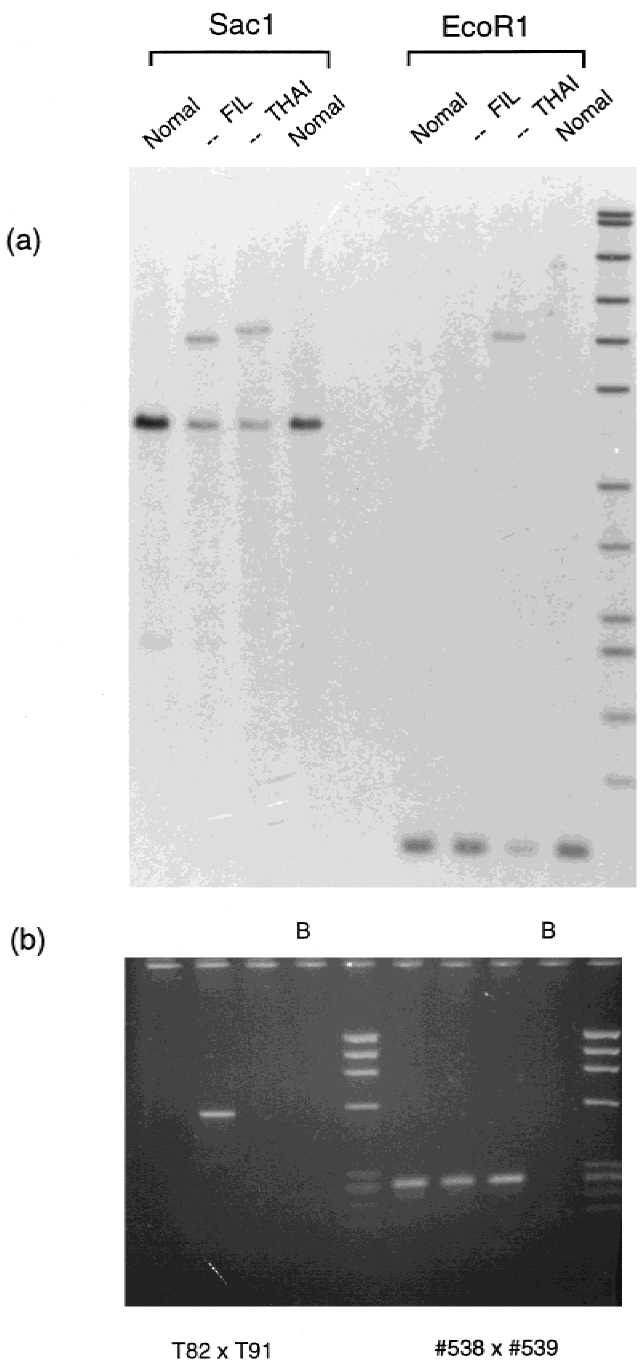

Fig. 1. (a): Southern blot of L0-specific fragments detected after digestion with *Sac*I and *Eco*RI clearly distinguishing 5′ breakpoint fragments of the $--^{FIL}$ and $--^{THAI}$ mutations as originally reported [2]. DNA samples were from individuals with $\alpha\alpha/\alpha\alpha$, $--^{FIL}/\alpha\alpha$, and $--^{THAI}/\alpha\alpha$ genotypes. (b): PCR analysis of the same samples [normal, $--^{FIL}$, $--^{THAI}$, and water blank (B)] with oligos T82 and T91 described in reference 4. As a control, oligos #538 and #539 amplify a normal fragment spanning the α-globin regulatory element HS-40 (Conditions and sequences available on request).

syndrome. Hence, it is important to develop simple, polymerase chain reaction (PCR)-based screening tests for all of these determinants of α thalassemia for routine evaluation of ''at-risk'' couples from Southeast Asia.

Ko et al. [3] have reported previously that the $--^{THAI}$ mutation occurs quite frequently in Taiwan using conventional Southern blot analysis [3]. More recently they reported a PCR-based strategy to identify the $--^{THAI}$ defect and, during the course of this study, characterized the chromosomal breakpoints of this deletion [4]. Surprisingly, these breakpoints differed from those originally reported [2] and more closely resembled those described for the $--^{FIL}$ mutation.

To resolve this discrepancy we reevaluated our previously published data [2] and confirmed our original mapping of the $--^{THAI}$ and $--^{FIL}$ breakpoints. In addition, we reanalysed DNA from the previously described family with the $--^{THAI}$ mutation and others with the $--^{FIL}$ mutation. As originally reported [2] L0-specific breakpoint fragments in SacI and *Eco*RI digested DNA most clearly distinguish between the $--^{THAI}$ and $--^{FIL}$ deletions (Fig. 1a). Thus it seemed possible that Ko et al. [4] had mistakenly characterized the $--^{FIL}$ rather than the $--^{THAI}$ determinant.

To test this we amplified DNA from the same patients analyzed by Southern blot using the PCR primers (T91 and T82) described by Ko et al. [4] (Fig. 1b). The 560 bp predicted gap-PCR fragment was amplified using DNA from a patient with the $--^{FIL}$ deletion but not the $--^{THAI}$ mutation. Analysis of DNA from several additional patients with the $--^{FIL}$ mutation confirmed that these primers specifically amplify the $--^{FIL}$ rather than the $--^{THAI}$ mutation. Further sequencing of the gap-PCR fragment from two patients with the $--^{FIL}$ mutation revealed, as predicted, an identical breakpoint sequence to that reported by Ko et al. [4] (data not shown).

It appears therefore that Ko et al. [4] have inadvertently characterized the $--^{FIL}$ rather than the $--^{THAI}$ mutation. Clearly this error could be important for those using these primers for prenatal testing and should prompt a reevaluation of previous studies reporting a high frequency of the $--^{THAI}$ mutation in Taiwan [3]. It seems possible that the $--^{FIL}$ rather than the $--^{THAI}$ mutation may be the more common of these two determinants of α thalassemia in this region.

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Fatal G-CSF-Induced Pulmonary Toxicity

To the Editor: Adverse effects of granulocyte colony stimulating factor (G-CSF) include bone pain, thrombocytopenia, hyperuricemia, vasculitis, Sweet's syndrome, anaphylactoid reactions, and liver damage. Pulmonary toxicity has been recorded in patients receiving GM-CSF alone [1], whereas lung toxicity in patients given G-CSF [1–5] together with other lung-damaging agents has been both suggested [4,5] and neglected [1,3]. Eighty-six patients were analyzed to find whether the coadministration of G-CSF and bleomycin results in enhanced pulmonary toxicity. No increase in the pulmonary toxicity of the combined regimen was found [1]. We describe the case of a 72-year-old physician who had anemia of 9.2 gr/dl, 4.4×10^9/L white blood cells (WBC) and 185×10^9/L platelets, and a normal chest X-ray film, and was given G-CSF unnecessarily (5 mg/Kg/day). Five days later, because of worsening of the dyspnea, increasing fatigue, and low oxygen saturation (70%), the patient was admitted to the intensive care unit where a chest X-ray disclosed diffuse bilateral alveolar opacities with a lower lung zone predominance (Fig. 1, left). The WBC was then 12.5×10^9/L and the bone marrow aspirate disclosed, in addition to granulocytic hyperplasia, 27% plasmocytes with an abnormal immunophenotype. The Bence Jones proteinuria was positive, but no paraproteinemia was found. A bronchioalveolar lavage showed bronchial cells and scant inflammatory cells, but the cultures, the *Mycobacterium tuberculosis* search by means of polymerase chain reaction, and the *Pneumocystis carinii*, herpes simplex, and cytomegalovirus search by means of fluorescent monoclonal antibodies, were all negative, as well as blood cultures. The patient was given hydrocortisone, cefotaxim, and co-trimoxazole, but the pulmonary lesions worsened requiring mechanical ventilatory support; a lung biopsy excluded infectious agents and showed organizing diffuse alveolar damage (Fig. 1, right). The patient died 17 days after starting the administration of G-CSF; he was always afebrile.

This case is similar to others describing pulmonary toxicity associated with G-CSF delivered together with other drugs endowed with pulmonary toxicity [1–5]. Causality of adverse events is difficult to determine, especially in cases for whom multiple confounders are present [3]. However, because no other agents were given to this patient, the case suggests that G-CSF alone can induce pulmonary toxicity resulting in hypoxemia, low oxygen saturation, and adult respiratory distress syndrome. Pulmonary toxicity by hemolymphopoletins was initially described for GM-CSF [4], this effect being more pronounced with the first dose [4]. It has been speculated that a release of vasodilators may produce a physiologic shunt in the lungs so that blood does not reach some oxygenated areas; however, the mechanisms underlying this side effect are unknown and may be mediated by the induction of secondary cytokine production such as tumor necrosis factor-alpha and/or interleukin-6. Because we were unable to find data on the pulmonary toxic effect of G-CSF alone and considering previous information describing lung toxicities of growth factors, this case should alert the medical community about the possibility of the pulmonary toxicity of G-CSF.

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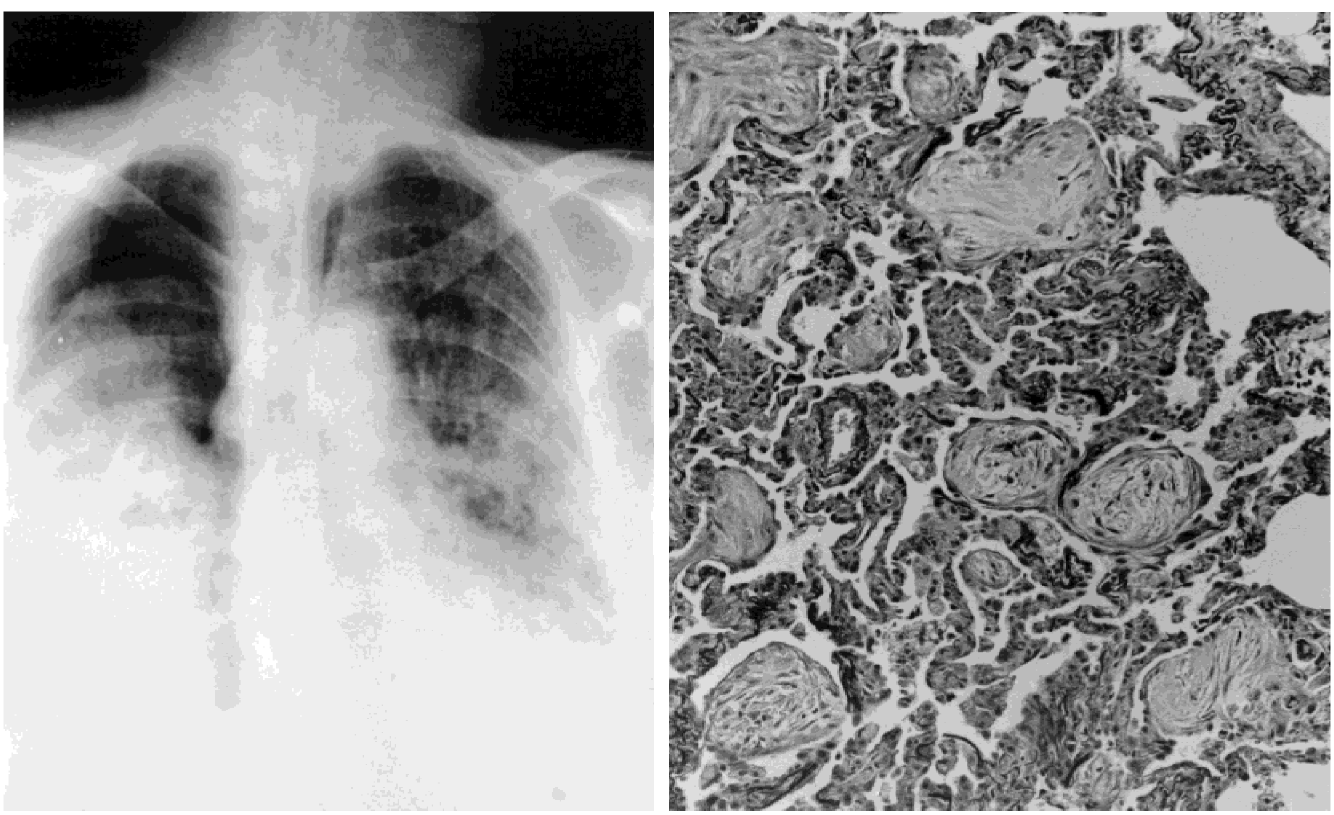

Fig. 1. Left panel: Chest radiograph shows diffuse bilateral alveolar opacities predominantly in the right lung. Right panel: Air space fibrosis in organizing diffuse alveolar damage. The incorporation of the exudate organizing along the alveolar septa is evident.

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The MERRF Mutation of Mitochondrial DNA in the Bone Marrow of a Patient With Acquired Idiopathic Sideroblastic Anemia

To the Editor: We proposed that the mitochondrial iron overload of ring sideroblasts in Pearson's syndrome and in acquired idiopathic sideroblastic anemia (AISA) is caused by a mitochondrial respiratory chain defect that leads to impaired reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) [1]. We also postulated that point mutations of mtDNA may be the cause of mitochondrial dysfunction in AISA and have recently been able to identify such mutations [2,3]. We have now detected a patient with AISA who carried in his bone marrow the A8344G mutation of mitochondrial $tRNA^{Lys}$, which is the well characterized cause of a mitochondrial encephalomyopathy called MERRF (myoclonic epilepsy with ragged red fibers) [4,5]. The 71-year-old man was incidentally found to have an immunoglobulin (Ig)A-kappa paraproteinemia in 1986. There was a low-grade lymphoplasmocytic bone marrow infiltration (20–30%) but no osteolytic lesions, lymphadenopathy, or hepatosplenomegaly. Neither the paraproteinemia nor the bone marrow infiltration progressed until the patient's death in 1995. The hematological workup in 1986 revealed abnormal ring sideroblasts in the bone marrow (ca. 10%). However, there was no significant anemia (hemoglobin [Hb] 13 g/dl). The white blood cell (WBC) (5,500/μl) and platelet counts (166,000/μl) were normal. We saw the patient again in 1992 because of anemia (Hb 9 g/dl, mean corpuscular volume [MCV] 111 fl). Platelet count was 97,000/μl. The leukocyte count was 3,400/μl, with a normal WBC differential. The bone marrow showed erythropoietic dysplasia with 20% ring sideroblasts, and a diagnosis of refractory anemia with ring sideroblasts was made (RARS [AISA]). The patient became transfusion-dependent in 1993. The bone marrow showed a slight increase in ring sideroblasts (25–30%) and in the degree of dyserythropoiesis. There was no progression to a more advanced type of myelodysplastic syndrome. The patient died in 1995 from a mesenteric infarction. He never presented neurological symptoms suggestive of MERRF syndrome or any other mitochondrial encephalomyopathy.

Total DNA was isolated from an archived bone marrow sample. Mitochondrial DNA was amplified in 17 overlapping segments using the polymerase chain reaction (PCR), with primer positions as previously reported [2]. PCR products were subjected to heteroduplex analysis with temperature-gradient gel electrophoresis (TGGE). Heteroduplex screening was positive in a 640-bp segment of mtDNA encompassing nucleotide positions 8282–8921 (Fig. 1). The pattern of intensity of the bands suggested that the proportion of mutated mtDNA in the bone marrow was approximately 50%. The mtDNA segment in question was cloned in *Escherichia coli* and sequenced with standard methods. Five of nine clones showed a point mutation characterized by an A → G transition at nt 8344. Because the patient had died in 1995 and the mutation was detected in archived material, we could not test other tissues for the presence of the mutation. Because the patient never showed any symptoms of MERFF syndrome, and because myelodysplastic syndromes are acquired clonal bone marrow disorders, we think that the MERRF mutation in this patient occurred in a hematopoietic stem cell which, after transformation by additional nuclear DNA mutations, gave rise to his bone marrow disorder.

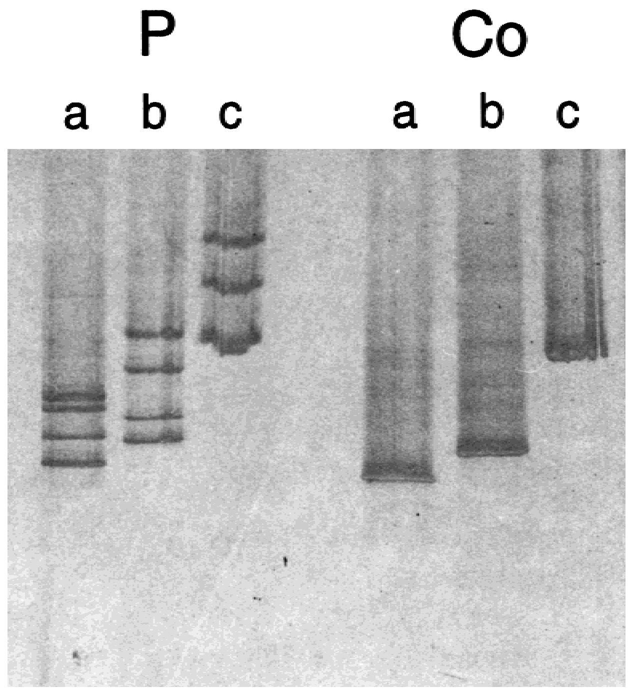

Fig. 1. Parallel TGGE. After denaturation and renaturation, the 640 bp PCR product was brought onto the gel in triplicate at time intervals of 15 min (lanes a, b, and c, respectively). A typical pattern of two heteroduplex bands (above) and two homoduplex bands (below) is seen in the patient (P), whereas only a normal homoduplex band is present in the control person (Co). Thin polyacrylamide gel (5%), containing 8 mol/L urea. Visualization of DNA bands by silver staining.

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Successful Hydroxyurea Treatment of a Patient With SD Hemoglobinopathy

To the Editor: Hydroxyurea (HU) reduces the number of pain crises in a significant percentage of patients with homozygous sickle cell disease [1]. We report herein a patient with hemoglobin (Hb) SD disease who had severe sickle pain crises that were eliminated by treatment with HU.

The patient is a 52-year-old woman of Indian and African heritage who had been hospitalized at least three to four times each year for treatment of pain crises. She reported frequent episodes of pain in her back and legs, which she managed with acetaminophen and codeine daily. In early 1993, she developed rheumatoid arthritis affecting the hands and was treated with methotrexate, 7.5 mg each week, and prednisone, 5 mg daily. While on this regimen she continued to have frequent and severe sickle cell pain crises. She had no palpable splenomegaly or joint deformities.

Laboratory evaluation at presentation showed: Hb, 9.0 g/dl; hematocrit, 29%; mean corpuscular volume (MCV), 85 μm^3; reticulocyte count, 4%; platelet count, 200,000/mm^3; and the white blood cell count (WBC), 11,000/mm^3, with a normal differential count. The diagnosis of SD_{Punjab} was confirmed by high performance liquid chromatography which showed 50.4% Hb D_{Punjab}, 43% Hb S, 3.6% Hb A_2, and 3.6% Hb F. Values for serum electrolytes, creatinine, and liver function tests were normal. During the subsequent 18 months, she was admitted seven times to the hospital for treatment of pain crises (Fig. 1) with parenteral meperidine. Also, during this time she used an average of 140 tablets of codeine and acetaminophen per month.

After discontinuation of methotrexate and prednisone for four weeks, treatment with HU was begun. While on HU at the starting dose of 1.0 g per day (15 mg/kg/day) her hematocrit fell, and the MCV and Hb F level increased. HU was briefly discontinued because of worsening anemia and thrombocytopenia. When her blood counts recovered, HU was restarted at 500 mg per day. Since then, her hematocrit has been in the range of 24–29%, her MCV around 100 and the WBC, platelet, and reticulocyte counts have been only slightly below the pretreatment values. Soon after initiation of treatment, the patient had a steady decrease in frequency and severity of sickle pain. After nearly two years of HU treatment at 500 mg per day she remains free of sickle pain crises, has discontinued the use of analgesic medications, and has had no visits to the emergency room or hospitalizations for pain crises.

In our patient, a relatively low dose of HU increased the fetal Hb from a pretreatment value of 3.6% to 11%. As expected, her MCV also increased, and her hematocrit was somewhat lower on treatment. Although changes in density and reticulocyte counts were observed in a preliminary

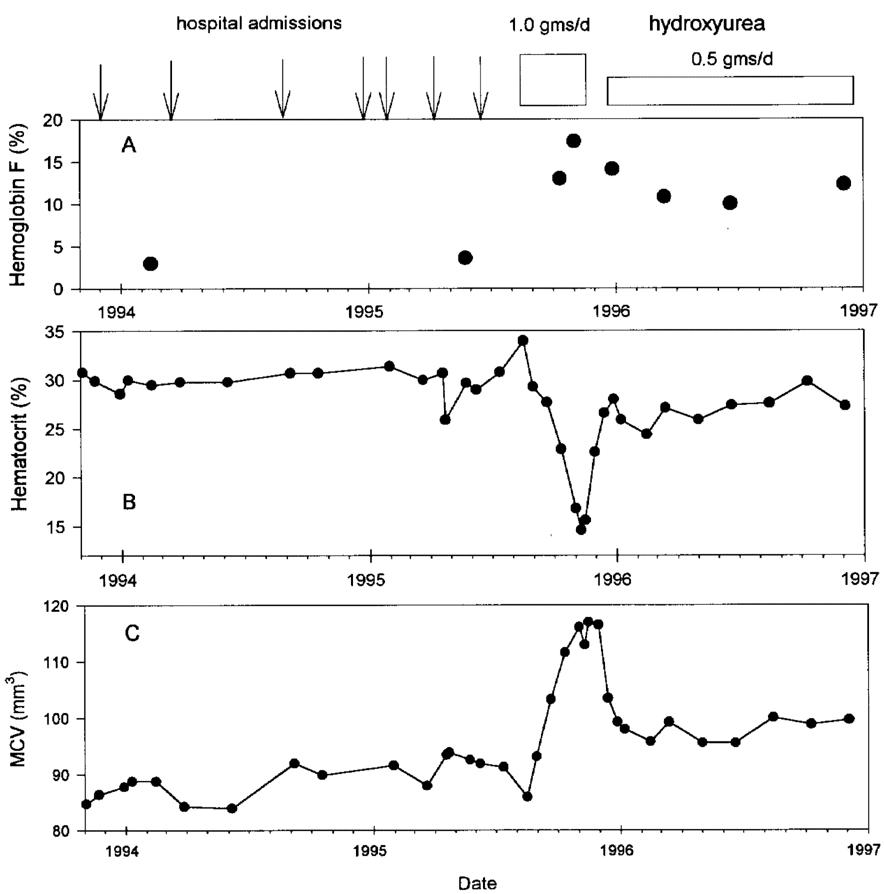

Fig. 1. Pre- and post-treatment values for percent of hemoglobin F (Panel A), hematocrit (Panel B), and MCV (Panel C). The arrows denote hospital admissions and the blocks show the daily dose of HU.

study of Hb SC disease patients treated with HU, improvement in clinical status could not be assessed [2]. Patients with $S\beta^{+}$ and $S\beta^{0}$ have been reported to experience improvement in well-being and Hb F levels on HU treatment [3–5]. Unsuccessful HU treatment of an adolescent with SO_{Arab} has also been described [4]. Our patient's gratifying response suggests that Hb SD disease patients with frequent pain crises may benefit from HU treatment.

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